REMARKS

Rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42 and 50-56 Under 35 U.S.C. § 103:

The Examiner has newly rejected Claims 1-3, 5, 10-27, 34, 37-38, 40-42 and 50-56 under 35 U.S.C. § 103, contending that these claims are not patentable over Lentz (U.S. Patent No. 6,231,536) and further in view of Selinsky et al. (*Immunology* 94:88-93, 1998) and Marakovsky et al. (U.S. Patent No. 6,017,527). Specifically, the Examiner submits that Lentz teaches a method and system for removing immunosuppressive components from the blood of mammals for treating diseases and conditions in deficiencies of the immune response, where blood is returned to the patient. The Examiner asserts that Lentz teaches a method to remove soluble receptors for TNF using ultrapheresis and an antibody immobilized using standard techniques for binding reactions to remove proteins from the blood. The Examiner states that Lentz does not specifically teach a recombinant monoclonal antibody specific for soluble receptors for TNFα covalently joined to a macroporous bead, but asserts that these deficiencies are made up for in Selinsky et al. and Marakovsky et al. The Examiner contends that Selinsky et al. teach antibodies specific for TNFRI, that TNFRI is removed by Ultrapheresis and that TNFRI effectively inhibits immune responses . The Examiner contends that Marakovsky et al. teach a method for stimulating an immune response in a patient by administering to a patient cells that have been bound by column chromatography. Therefore, the Examiner contends that it would have been *prima facie* obvious to use the method of Lentz to stimulate an immune response with antibodies to sTNFRI for the removal of sTNFRI which inhibits an immune response as taught by Selinsky et al. and immobilize the antibody to a macroporous bead as taught by Marakovsky et al.

Applicants traverse the Examiner's rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42 and 50-56 under 35 U.S.C. § 103. First, it is submitted that U.S. Patent No. 6,231,536 to Lentz is not effective prior art against the claimed invention because the claimed subject matter was invented by the present inventors prior to the effective date of U.S. Patent No. 6,231,536. Enclosed herewith is a Declaration under 37 CFR § 1.131 executed by all of the present inventors. This Declaration provides evidence of: (1) conception of the claimed invention at a date prior to the earliest priority filing date of U.S. Patent No. 6,231,536 (e.g., May 22, 1998); and, (2) diligence in reducing the claimed invention to practice from a date prior to the earliest priority filing date of U.S. Patent No. 6,231,536 to the date of constructive reduction to practice of the claimed invention. As required by

37 CFR § 1.131, the Declaration affirms that the acts relied upon to establish conception and diligence were carried out in the United States. Therefore, Applicants submit that Lentz is not an effective reference against the present claims.

With regard to Selinsky et al. and Marakovsky et al., Applicants submit that neither of these references, alone or in combination, teach or suggest the present invention for the reasons of record.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42 and 50-56 under 35 U.S.C. § 103.

Supplemental Information Disclosure Statement:

Applicants enclose herewith a Supplemental 1449 form and Information Disclosure Statement and copies of references that were cited less than three months prior to this submission in an International Search Report for the corresponding international application.

Applicants submit that the presently claimed invention is patentable over any of the references cited in the International Search Report. In order to expedite prosecution, the following discussion of the references is provided.

Japanese Publication No. 02045064, published February 15, 1990 :

This abstract is a publication of the English abstract and one drawing from Japanese Application No. 6319294, filed August 2, 1988. The abstract discloses a method for removal of soluble interleukin 2 receptor (IL2R) from blood by adsorbing and fixing a monoclonal antibody against sIL2R to a hollow yarn membrane and bringing the blood and/or plasma from a patient into contact with the hollow yarn membrane. The plasma from which the sIL2R is removed is mixed with the concentrated blood from which the plasma was initially separated and is returned to the patient.

Initially, Applicants submit that the claims, as amended, are not anticipated by Japanese Publication No. 02045064 (English abstract from Japanese Application No. 6319294), since the publication does not teach or suggest contacting an acellular component of blood or a fraction thereof with a binding partner that selectively binds to soluble receptors for tumor necrosis factors α and β, interleukin-1 receptor antagonist, soluble receptors for interferon-γ, and soluble receptors for interleukin-1, or soluble receptors for interleukin-6.

Moreover, it is submitted that it would not be obvious to modify the method disclosed in Japanese Publication No. 02045064 to arrive at the claimed invention, because there is no teaching or suggestion provided in the abstract of Japanese Publication No. 02045064 to remove any molecule other than IL2R. Furthermore, at the time of the present invention, several teachings in the art, together with Japanese Publication No. 02045064, would discourage researchers from the general approach of Japanese Publication No. 02045064 for immune response stimulation. Specifically, other investigators have shown that soluble IL-2R is a truncated form of the membrane receptor that binds to IL-2 with low affinity (see, e.g., Jacques et al., 1987, *J. Immunol.* 139:2308-2316; Loughnan and Nossal, 1990, *J. Mol. Cell. Immunol.* 4:307-315; abstracts provided). Despite earlier speculation that this receptor might compete with the membrane form of the receptor for binding to IL-2, and thus be an immune response inhibitor, investigators have shown that sIL-2 binds with such low affinity to IL-2 that it does not effectively compete with the membrane form (Loughnan and Nossal, *ibid.*). Indeed, addition of large quantities of sIL-2R to cultures of T cells fails to inhibit the response of those T cells *in vitro*, and removal of sIL-2R from human patient tumor ascites failed to reverse lymphocyte suppression observed prior to removal of the sIL-2R (Elg et al., 1997, *Gynecol. Oncol.* 66:133-137; abstract provided). Together, these data have demonstrated that removal of sIL-2R does not provide any immune response stimulation, as is claimed. Therefore, Applicants submit that one of skill in the art would have no motivation to use the method disclosed by Japanese Publication No. 02045064 or to further modify the publication to be in accord with the present claims, since there is no apparent therapeutic benefit to be obtained. Indeed, one would be dissuaded from doing so.

In contrast to the above-described disadvantages of targeting a soluble IL-2R, the present invention, as currently claimed, provides advantages that further distinguish the claims from the prior art. Specifically, in the method of the present claims, the immune system inhibitors that are targeted are inhibitors that interfere primarily with the elaboration of macrophage function, which is believed to have advantages over the targeting of other immune response inhibitors. Activated macrophages play a pre-eminent role in the initiation and development of the immune response (reviewed by Mantovani, et al., 2001, Novartis Foundation Symposium 234:120-131, and Bancroft, et al., 1994, Immunology Letters 43:67-70). Macrophages, once activated, participate in the elimination of a pathogenic agent through the release of nitrogen and oxygen radicals and degradative enzymes or, in the case of cellular targets, through the release of tumor necrosis factor which induces apoptosis.

Moreover, activated macrophages release a host of mediators that contribute to the development of the inflammatory response and that recruit additional immune cells (leukocytes) to the site at which the pathogenic agent is present. For example, tumor necrosis factor-α (TNF-α), once produced by activated tissue macrophages, alters nearby blood vessels resulting in the accumulation of fluid and the recruitment of additional leukocytes to the anatomical site where the TNF-α initially was released. Interleukin-1, which also is produced by activated macrophages, encourages the activation of the infiltrating leukocytes. Additionally, it exerts systemic effects through its action on the hypothalamus. Interleukin-6, another product of activated macrophages, also exerts a systemic effect by stimulating the liver to produce additional mediators of inflammation, tissue repair, and wound healing. Collectively, these mediators initiate the local inflammatory response and permit its evolution, and they coordinate systemic effects and leukocyte recruitment, both of which participate in the elimination of the pathogenic agent.

Each of the immune system inhibitors of the claimed invention has the ability to interfere either with the activation of macrophages or with the elaboration of activated macrophage function. Soluble interferon-γ (IFN-γ) receptor, by virtue of binding interferon-γ and preventing its engagement of the membrane interferon-γ receptor, blocks the activation of macrophages by interferon-γ, the most potent mediator for this purpose. Thus, macrophages are less likely to contribute directly to the elimination of the pathogenic agent or to initiate and perpetuate inflammatory processes. Similarly, the presence of soluble receptors for tumor necrosis factor potentially will inhibit the induction of apoptosis in cellular targets and will block TNF-induced changes in the vasculature, which will prevent the recruitment of additional leukocytes. Soluble interleukin-1 receptors and interleukin-1 receptor antagonist both block the ability of interleukin-1 to enhance the activation state of the recruited leukocytes and, like soluble interleukin-6 receptors, block systemic effects attributable to interleukin-1 and interleukin-6, respectively. Thus, these immune system inhibitors block the actions of immune system stimulators that are at the root of the developing immune response. Therefore, not only are these initial events blocked by this particular collection of immune system inhibitors, but so are all of the secondary and later events which normally ensue. By targeting these particular immune system inhibitors for removal by the claimed invention, these primary functions will be enhanced and their enhancement will lead to the full

elaboration of the downstream immunological events necessary to effect the elimination of the pathogenic agent.

PCT Publication No. WO 96/16666, published June 6, 1996:

This PCT publication discloses an immunoadsorption method for subtracting selected pathogenic factors (e.g., HIV antigens, TNF-α, interleukins IL1β, IL4, IL6, IL8, IL10, soluble HLA molecules, or other factors whose presence is increased during HIV infection). The method includes drawing blood from a patient, absorbing the pathogenic factors that are present in the blood by using specific ligands against the factors in order to obtain blood featuring a low concentration of pathogenic factors.

Initially, Applicants submit that the claims, as amended, are not anticipated by PCT Publication No. WO 96/16666, since PCT Publication No. WO 96/16666 does not teach or suggest contacting an acellular component of blood or a fraction thereof with a binding partner that selectively binds to soluble receptors for tumor necrosis factors α and β, interleukin-1 receptor antagonist, soluble receptors for interferon-γ, and soluble receptors for interleukin-1, soluble receptors for interleukin-6, and soluble receptors for interleukin-8.

Moreover, Applicants submit that it would not be obvious to modify the disclosure of PCT Publication No. WO 96/16666 to arrive at the claimed invention. PCT Publication No. WO 96/16666 is specifically directed to the removal of pathogenic factors and of cytokines that are believed to enhance acquired immunodeficiency from the blood of HIV-infected patients. Indeed, the cytokines that are taught to be removed by PCT Publication No. WO 96/16666 encompass most of the cytokines for which the present invention intends to increase the activity (i.e., by removing the soluble receptors for these cytokines that would inhibit the activity of the cytokines). Therefore, PCT Publication No. WO 96/16666 teaches a goal that is opposite from the present invention, and does not provide any suggestion or motivation to arrive at the claimed invention.

Applicants have attempted to respond to the Examiner's concerns as set forth in the August 10 Office Action. It is submitted that all claims are allowable and it is requested that the Examiner pass this case to issue. In the event that the Examiner has any questions or concerns regarding the

allowability of the claims, it is requested that this be considered a conditional request for a telephone interview, and the Examiner is encouraged to contact the below-named agent.

Respectfully submitted,

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Marked-up Version Showing Amendments

Claims 10 and 11 have been canceled.

Claims 1 and 42 have been amended as shown below.

1. (Twice Amended) A method of stimulating an immune response in a mammal having a pathological condition, comprising:

a. obtaining whole blood from the mammal;

b. separating the whole blood into a cellular component and an acellular component or a fraction of the acellular component, wherein said acellular component or said fraction of the acellular component contains a targeted immune system inhibitor selected from the group consisting of soluble receptors for tumor necrosis factors α and β, interleukin-1 receptor antagonist, soluble receptors for interferon-γ, soluble receptors for interleukin-1, and soluble receptors for interleukin-6;

c. contacting the acellular component or said fraction of the acellular component with a binding partner capable of specifically binding to said targeted immune system inhibitor;

d. removing the binding partner bound to said targeted immune system inhibitor from said acellular component or said fraction of said acellular component to produce an altered acellular component or altered fraction of the acellular component having a reduced amount of the targeted immune system inhibitor;

e. combining the cellular component with the altered acellular component or altered fraction of the acellular component to produce altered whole blood; and

f. administering the altered whole blood to the mammal.

42. (Twice Amended) A method for stimulating an immune response in a mammal having a pathological condition, comprising:

a. obtaining a whole blood from a mammal;

b. separating the acellular component or a fraction of said acellular component of the whole blood from the cellular component of the whole blood, said acellular component or said fraction of the acellular component containing a targeted immune system inhibitor selected from the group consisting of soluble receptors for tumor necrosis factors α and β, interleukin-1 receptor antagonist, soluble receptors for interferon-γ, soluble receptors for interleukin-1, and soluble receptors for interleukin-6;

c. contacting the acellular component or fraction of said acellular component containing the targeted immune system inhibitor with at least one antibody capable of specifically binding to the targeted immune system inhibitor, wherein the antibody is attached to an inert medium to form an absorbent matrix;

d. removing the absorbent matrix comprising the antibody bound to the targeted immune system inhibitor from the acellular component or fraction of the acellular component to produce an altered acellular component or altered fraction of the acellular component;

e. combining the altered acellular component or altered fraction of the acellular component with the cellular component to produce an altered whole blood; and

f. administering the altered whole blood to the mammal.